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EDITORIAL

Editorial for the special issue neurotrophic factors

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This "Cell and Tissue Research" Special Issue focuses on the cell biology of neurotrophic factors. Why this is important? Neurotrophic factors (NTFs) are secreted proteins that by binding to their specific receptors on the plasma membrane of neurons activate intracellular signalling pathways that regulate several key aspects of neuronal structure and function as well as survival. Four classes of neurotrophic factors have been characterized so far. The oldest is the neurotrophin family represented by the first growth factor described – nerve growth factor (NGF)—and by the most studied trophic factor brain-derived neurotrophic factor (BDNF). Other members of the neurotrophin family are neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4/5).

The second family of NTFs is heralded by the glial cell line-derived neurotrophic factor (GDNF) whose biology has been much studied, in part because it has special relevance to dopamine neurons of the substantia nigra pars compacta that degenerate in Parkinson's disease. Several clinical trials have explored GDNF actions in Parkinson's disease patients. Other members of the GDNF family of ligands (GFLs) are neurturin (NRTN), artemin (ARTN) and persephin (PSPN). The most recent addition to the family, Growth/Differentiation Factor 15 (GDF15), shows structural similarity and uses the same receptor system as other members of the GDNF family.

The neuropoetic cytokine (neurokine) family (also known as interleukin 6 (IL-6)) or glycoprotein 130 (GP130) consists of several factors, of which the best known are IL-6, ciliary neurotrophic factor (CNTF) and the cardiotropins 1 and 2 (CT1 and CT2).

The cerebral dopamine neurotrophic factor (CDNF)—mesencephalic astrocyte-derived neurotrophic factor (MANF) (CDNF-MANF)—family of neurotrophic factors is the newest defined and evolutionarily most conserved. Interestingly, this family differs significantly from the others by its members acting not only after secretion but also, and mostly, inside the cells in the endoplasmic reticulum.

Neurotrophin, GFL and neurokine family members signal through the transmembrane receptor tyrosine kinases or through receptors that interact with kinases. The specific neuronal populations responsive to neurotrophic factors express cognate receptors at the cell surface whose activation acts through well-defined pathways to trigger a wide variety of biological responses. Events are registered in the cytosol, ranging from changes in the synthesis and trafficking of intracellular proteins and vesicles, as well as in the nucleus with potent effects in regulating transcription. NTF signalling is best understood in the context of the cells in which they signal to regulate proliferation, differentiation, migration, axonal growth, survival of developing neurons, maintenance of adult neurons, and synaptic plasticity. Neurotrophic factors are thus crucial for the development, physiological regulation and maintenance of the nervous system, but also act on non-neuronal cells.

Since NTFs regulate neuronal survival, regeneration and responses to toxic exposure and injury, they have been evaluated as candidate drugs for the treatment of various neurological diseases, including neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS). Remarkably, fully 30 years after initiating the first clinical trials with NTFs none have been approved for treating patients. Indeed a recently concluded series of trials employing antibodies to NGF for Osteoarthritis may be the first to achieve approval for an NTF-related treatment. One of the reasons for such slow progress is limited knowledge about the cell biology of NTFs, especially in the context of brain aging and disease. Why is there such a knowledge gap? There are several reasons.

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Firstly, the nervous system is by far the most complex organ; the brain harbors 10^{11} neurons engaged in at least 10^{14} synaptic contacts. NTFs thus act to instruct and support a complex machine whose functions are highly diverse. Secondly, neurons are postmitotic cells taxed by the need to adapt their function – i.e. to demonstrate plasticity and achieve homeostasis – in the context of a changing external environment as well as to systemic changes, such as those that occur with normal and disease-related aging. This implies that actions of NTFs are often context-dependent and can thus not be readily generalized to all developmental stages and throughout all brain areas. A key feature of context is location. It is increasingly recognized that studying secretion and actions of NTFs must consider the neuronal compartment(s) – i.e. context – in which the events are triggered. Thirdly, neuronal morphology is rather unique with long axons and dendrites. For example, in the case of midbrain dopamine neurons as many as 500,000 synaptic contacts are sustained at relatively great distances from the neuron cell body. Neuron cell bodies are thus charged with overcoming the logistical challenges for supplying the molecular machinery needed to support distant synapses. NTF actions are thus tailored to support neurons in meeting these challenges. Fourthly, the physiological and anatomical burdens imposed upon neuron function come with extraordinary energy needs, especially those necessitated by the firing of action potentials and long distance trafficking of vesicles and molecular cargoes. Indeed, possibly most challenging is the need to initiate and respond to chemical and electrical signals acting at synapses whose structure and function vary greatly. NTFs play critical roles in enabling neurons to meet each of these challenges and thus to secure their ability to function over many decades in some mammals.

This Special Issue attempts to summarize current knowledge on the cell biology of NTFs. It comprehensively addresses: NTF synthesis, processing, secretion, receptor activation, and endocytosis, downstream signalling, and actions in supporting neuronal growth, maintenance, synaptic plasticity, and survival, as well as changes in NTF biology posed by disease.

Two papers describe the current state of knowledge regarding synthesis, trafficking and release of BDNF. The paper by Brigadski and Leßmann (2020) comprehensively reviews each of several important features, and points to a diverse set of neuronal and non-neuronal cells that participate in BDNF synthesis and release. Indeed, several cell types in brain and the periphery serve as sources of BDNF. One interesting perspective is the possibility that BDNF released from CNS neurons may act on cells outside the brain, and vice versa. Within the brain, it is clear that neurons as well as astrocytes and microglia can all serve as a source for BDNF. Equally significant is the perspective that both development and cellular context are important for defining the mechanisms and loci for BDNF release. The paper by Kojima and colleagues (2020) explores the biology of BDNF with an emphasis on the methods now available for detecting and measuring the relatively small amounts present in and released from cells. Loci for BDNF release can now be interrogated much more effectively and both pre- and postsynaptic domains are clearly engaged. Furthermore, the synaptic machinery for release is now much better defined. Taken together these papers highlight emerging data pointing to the complexity and specificity of mechanisms that regulate BDNF availability for its responsive cells.

Andreska and colleagues (2020) focus on regulation of TrkB surface expression as a major factor for modulating neuronal responsiveness to BDNF. Pointing to co-factors such as cAMP, N-glycosylation and contributions from G protein-coupled receptors (GPCR) to explain signaling differences between TrkB and other Trk family members, the authors review contexts wherein intracellular TrkB pools are rapidly mobilized to surface membranes, for example at pre- and post-synapses in response to activity. One particularly interesting locus of BDNF action is the dendritic spine. BDNF has key roles during the lifetime of dendritic spines, from biogenesis to maintenance and plasticity, and spanning embryonic development and the adult. Zagrebelsky et al. (2020) review the roles of BDNF in modulating synapse number, structure and plasticity via apparently opposing roles of its receptors, TrkB and $p75^{NTR}$, with consequences for learning/memory, emotional regulation, and age and disease-related cognitive impairment. As an example for the complex involvement of BDNF pathways in regulating learning and memory processes, Meis and colleagues (2020) describe the current knowledge how BDNF signalling in amygdala neuronal circuits steers fear learning and fear extinction. Taking into account intra-amygdalar expression and release of BDNF but also release at thalamic and cortical inputs to the basolateral amygdala (BLA), the authors try to disentangle how proBDNF/$p75^{NTR}$ and mBDNF/TrkB signalling in glutamatergic principle cells and GABAergic interneurons of the amygdala, respectively, shape fear memories in cooperation with hippocampal and cortical synaptic circuits.

Johnstone and Mobley (2020) take up the issue of BDNF actions in shaping activity of neuronal circuits by emphasizing that BDNF/TrkB signalling can considerably differ between distinct neuronal compartments even within the same cell. Moreover, by pinpointing the different well-known intracellular signalling cascades downstream of TrkB activation, the authors lead us through changing aspects of these signalling events during neuronal development, initial circuit formation, and synaptic plasticity-dependent memory formation in adulthood.

Several reviews discuss GDNF and the cell biology of its receptors. John M. Spitsbergen and his team discuss GDNF

synthesis, secretion and internalization and focus on cellular events activated by GDNF on motoneurons (Cintrón-Colón et al., 2020). Masahide Takashashi discovered the RET proto-oncogene and he and his colleague present a comprehensive view of GFL signalling via the RET receptor (Kawai and Takahashi, 2020). Carlos F. Ibañéz originally demonstrated that GDNF can signal RET-independently and identified NCAM as one of the receptors used by GFLs. In the current review Ibañéz and colleagues (2020) summarize current knowledge on GFL non-RET signalling, focusing mostly on cellular effects. Donnelly & Pierchala (2020) discuss the role of plasma membrane and the localization of GFL receptor components in GFL signaling and crosstalk with other neurotrophic factor receptors and how trafficking of GFL receptor components potently influence the function of these other neurotrophic factors. They stress that complex signaling interactions are to be considered when evaluating the potential pathophysiological roles of RET, Trks and p75 in cancer and neurodegenerative disorders.

GDNF has prominent survival promoting and neurorestorative effects on midbrain dopamine neurons that degenerate in Parkinson's disease. Although the effects of exogenously added GDNF on dopamine neurons are very well documented, the role of endogenous GDNF and its receptors GFRα1 and RET are still under investigation. Edgar Kramer and colleagues (2020) discuss the phenotypes in knockout mice for GDNF and its receptors'. Importantly, this review summarizes data on the crosstalk of GFLs with genes mutated in familial forms of Parkinson's disease, such as PINK1, Alpha-synuclein, DJ-1, etc. Don Gash pioneered GDNF clinical trials in Parkinson's disease (PD) patients and in this review he summarizes the results of GDNF clinical trials and explores the reasons why the clinical benefit of GDNF treatment failed to meet specified clinical endpoints (Gash et al. 2020). Gene therapy employing neurturin in clinical trials in PD also failed to demonstrate efficacy. In order to improve therapeutic efficacy, several groups have used site-directed mutagenesis and gene technology to produce GDNF and NRTN variants with improved therapeutic properties. Pia Runeberg-Roos and Richard Penn in their review (2020) summarize biochemical and animal data for improving the therapeutic potential of mutated GDNF family ligands. GFL proteins are not ideal for the treatment of neurological diseases, mainly because they do not pass through the blood–brain barrier and therefore should be delivered directly into the brain using complicated neurosurgery. To overcome this limitation small molecules that mimic the action of GFLs have been developed. In the review by Arun Mahato and Yulia Sidorova (2020), recent progress in developing small molecule RET agonists for the treatment of pain and Parkinson's disease is discussed.

As mentioned above CDNF-MANF family is an unconventional family of NTFs that signal mostly inside the cells regulating ER stress, but as these proteins are also secreted into the extracellular space, there is another mode of signalling that is initiated from the plasma membrane. In their review Brandon Harvey and his colleague discuss recent progress in CDNF and MANF signalling in the ER (Jäntti and Harvey 2020).

Overall, this special issue brings together the expert current knowledge on the biology of NTFs. Topics range from the role of BDNF in synaptic plasticity and how it contributes to memory formation, to cutting edge information on the signalling cascades employed by diverse GDNF neurotrophic factor family members, and to many new insights into the unconventional cellular actions of CDNF-MANF family neurotrophic factors. Now, many decades after the discovery of the first NTF and nearly four decades after the appreciation of the existence of many additional NTFs acting on a host of target cells, we embark on an era in NTF research – one in which new tools and concepts will guide us to a more incisive understanding of NTF actions in the normal nervous system and a more comprehensive appreciation of how they feature in the biology of disease. Our shared hope is that this will also be an era unprecedented for the creation of approaches to exploit NTFs as treatments for neurodegenerative diseases.

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